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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,988	BULAJ, GRZEGORZ	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40* is/are rejected.

7)☒ Claim(s) *1,13 and 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-4-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-44 are pending.

The following Office action is applicable to the pending claims 1-44.

IDS

The references listed in IDS filed 4 November 2002 have been considered.

Objection to claims

The disclosure is objected to because of the following informalities:

(1) In page 2, line 24, "CMTI" and "EETI"; should be spelled out in full at the first instance of use. See also page 5, line "HPLC"; and, page 13, line 19 "RT", line 21, "TFA, and line 22, "ACN".

(2) In page 3, line 22, "glutathione (reduced GSH and oxidized GSSG)" should be changed to "glutathione (reduced form, i.e., GSH, and oxidized form, i.e., GSSG)".

(3) In page 10, line 20, "tris" should be changed to "Tris".

(4) In claims 1, 13 and 25, "5-55 amino acid residues" should be changed to "5 to 55 amino acid residues".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "containing two or more cysteines"; the recitation is unclear regarding to which subject, the peptide fragment consisting of 5 to 55 amino acids, or the peptide recited in the claim which comprises the peptide fragment, said "containing" is directed. Note that claim 1 recitation "comprises 5-55 amino aid residues …" is an open-ended; thus, the full-length peptide encompasses heterologous sequence other than the peptide fragment consisting of 5 to 55 residues thereof. Claim 1, item *b*, sets forth the limitation "the resulting mixture"; there is insufficient antecedent basis for this limitation in the claim. Also, claim 1 is indefinite because it is unclear with regard to whether or not said resulting mixture refers to (i) combination between the refolding mixture and the peptide, or combination of the peptide with a non-ionic detergent or/and a redox reagent. See also claims 13 and 25. The dependent claims are also rejected.

Claim 2 recites "a cosolvent"; the recitation is not apparent regarding whether or not the said cosolvent refers to small organic cosolvent or a polymer cosolvent because the specification does not define what the cosolvent is. See also claims 14 and 28.

Claim 3 is indefinite in "mixture thereof" because the claim does not make it clear as to what are components of said mixture; does it refer to a mixture produced from combination of polyoxyethylenes or/and polyoxyethylene derivatives or/and alkyl derivative of carbohydrates? Additionally, claim 3 recitation "alkyl derivatives of carbohydrates" is unclear as to whether or not the carbohydrate (a *generic term*) encompasses ketose (e.g., dihydroxyacetone) or chitin in addition to monosaccharide, disaccharide or polysaccharide. See also claims 15 and 29.

Claim 6 is indefinite because "primary, secondary, tertiary" are not solvents; "allylic" and "poly-" are incomplete recitations in that they do not identify any solvents. Also, claim 6 is indefinite in the recitation "mixture thereof" because the recitation is unclear as to which compounds cited in the Markush group of the claim are components of the said mixture. In addition, claim 6 is unclear in the term "poly-" (line 4 of the claim); to what does this prefix refer? See also claims 18 and 32.

Claim 13, item *a*, recites "a concentration from about 0.1 μM to about 100 mM"; sub-item (i), recites "an amount from about 0.001% to abound 90%"; and sub-item (ii) recites "an amount from about from 0.01 mM to about 25 mM". These recitations are indefinite because the term "about" setting forth with a very broad range (0.001 to 90, 0.001 to 90, and 0.01 to 25) renders the claim indefinite since "about 0.001" can read on "near zero", and "about 90" can read on "99", for example. See also claim 14.

Claim 21 as written appears to set forth no further limitation to claim 20 from which claim 21 depends. Thus, claim 21 is unclear as to what limitation the claim recites.

Claim 25 recites "synthesizing a peptide"; the recitation is not apparent as to whether or not the said "synthesizing" refers to *chemical* synthetic process or *biosynthetic* process. The dependent claims are also rejected.

Claim 39 recites "isoteric lactam"; this recitation has not been defined in the specification. It is therefore unclear regarding whether or not the recitation refers to any of a group of cyclic amides characterized by the NHCO group. Also, claim 39 is unclear as to "ester-thioether replacements"; does it refer to ester being replaced by thioether linkage or thioether linkage being replaced by ester bond? See also claims 41 and 43.

Claim 40 is indefinite in the recitation "replacement is selected from the group consisting of Ser/(Glu or Asp), Lys/(Glu or Asp), Cys/(Glu or Asp) and Cys/Ala combinations" because the specification does not provide sufficient definition of this recitation, and because it is unclear as to (*i*) which kind of chemical bonding between Cys and Ala (note that Ala side chain contains no chemically active group), and (*ii*) Ser/(Glu or Asp) does not clearly establish a chemical linkage between Ser and Glu or between Ser and Asp since chemical bonding between Ser and Glu or Ser and Asp can be either ester linkage or hydrogen bonding; See also "Cys(Glu or Asp)". Thus, clarification in this regard is needed. Further, claim 40 is unclear in "Cys/Ala combinations"; what is said combination? See also claims 42 and 44.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-4, 8 and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Gellman, S. H. et al. (US pat. No. 5563057).

Gellman et al. teach a method of refolding a peptide that contains disulfide (see abstract). The method comprises adding the peptide to refolding reagent comprising (i) a redox regent and (ii) non-ionic detergent (e.g., Triton X-100) (see Examples III, IV and VI). Note that Triton X-100 is polyoxyethylated octyl phenol. Gellman et al. teaching meets the limitations set forth in claims 1 and 3-4. Since Gellman et al. teach that the instant invention, i.e., method for refolding misfolded protein with detergent, is applicable to peptide hormone (see column 4, lines 65-68) wherein insulin and relaxin are such small disulfide-containing peptide hormones, for example. Thus, Gellman's patent anticipates claims 1 and 3-4 of the current application.

Gellman et al. teach β-cyclodexrin (β-CD) acts as a cosolvent (see column 5, lines 10-15), as applied to claim 2 of the current application.

Gellman et al. teach that redox agent is dithiothreitol (DTT) that can adapts either oxidized form or reduced form (see O'handley, D. (2002) *Application Note*). Thus, the above Gellman teaching is applied to claim 8 of the instant application.

Also, Gellman et al. teach that refolding reaction is performed at pH 8.0 (see Example III), which meets that limitation set forth in claim 11 of the current application. Since the refolding reaction is performed at room temperature (e.g., 25 °C), Gellman et al. teaching also meets the limitation set forth in the application claim 10.

Claims 1-4, 6-11 and 25, 27-28, and 32-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Cerietti, N. et al. (EP 433225, June 19, 1991).

Cerietti et al. teach a method of refolding a peptide that contains disulfides from an aggregated form (see the patent claims 1-2 and 14) comprising (**a**) the peptide being subject to the refolding condition comprising (i) a mild detergent which is non-ionic detergent (see the patent claims 3 and 19-20) and (ii) a sulfhydryl/disulfide redox reagent (see the patent claim 15), and (**b**) incubating said peptide with the refolding reagents comprising the components of (i) and (ii) in order for refolding said peptide, as applied to claim 1 of the current application. Note that Cerietti et al. patent is an anticipatory art over the instant disclosure *because* claim 1 sets forth that the peptide which comprises 5 –55 amino acids; such the claim language is open-ended and renders the claim so broad that it encompasses a heterologous portion(s) in addition to the peptide fragment of 5 to 55 amino acids, and *because* the peptide of Cerietti et al. is sulfhydryl/disulfide-rich (see page 18).

Cerietti et al. teach a detergent-assisted polypeptide refolding which employs non-ionic detergent, e.g., *Tween* that is a polyoxyethylene derivative, as applied to the application claims 3-4.

Cerietti et al. teach a method of refolding a polypeptide that contains disulfides from an aggregated form (see the patent claims 1-2 and 4) comprising (**a**) producing the polypeptide via biosynthesis (see the patent claim 4); (**b**) isolating the polypeptide in an insoluble aggregate fraction (see the patent claim 5); (**c**) the polypeptide being subject to the refolding condition comprising (i) a mild detergent which is non-ionic detergent (see the patent claims 3 and 19-20) and (ii) a sulfhydryl/disulfide redox reagent (see the patent claim 15); (**d**) incubating said peptide

with the refolding reagents comprising the components of (i) and (ii) in order for refolding said polypeptide, and (e) purifying the polypeptide by chromatography (see the patent claim 32). The above Cerietti et al. teaching is applied to claims 25 and 27 of the current application.

Note that Cerietti et al. patent is an anticipatory art over the instant claims *because* claim 1 sets forth that the peptide which comprises 5 –55 amino acids; such the claim language is open-ended and renders the claim so broad that it encompasses a heterologous portion(s) in addition to the peptide fragment of 5 to 55 amino acids, and *because* the peptide of Cerietti et al. is sulfhydryl/disulfide-rich (see page 18), and the Cerietti's polypeptide comprises the sulfhydryl/disulfide-rich peptide fragment (see page 18). Therefore, Cerietti et al. patent is an anticipatory art over claim 25 of the current application.

Cerietti et al. teach that the solubilizing agent for said refolding condition comprises a cosolvent (see the patent claim 23), as applied to the application claims 2 and 28. The said cosolvent is ethanol or isopropanol (see page 5, line 58), as applied to the application claims 6 and 32.

Cerietti et al. teach that the redox reagent is oxidized and reduced form of glutathione, cysteine or 2-mercaptoethanol (see the patent claim 15), as applied to the application claims 7-9 and 33-35.

Also, Cerietti et al. teach that the refolding reaction is performed at pH of about 6-10 and a temperature of about 0 °C to about 37 °C (see the patent claim 14), as applied to the application claims 10-11 and 36-37.

Claims 1-4, 6-8, 10-11, 13-16, 18, 20 and 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Builder S. et al. (US Pat. NO. 5756672) as is evidenced by the reference incorporated (see EP 433225 indicated at column 4, line 47).

Builder et al. teach a method of refolding cysteine-rich peptides, e.g., relaxin (chains A and B) (see column 9, line 22), which is misfolded and denatured (see abstract). The method comprises: (**a**) reacting the peptide of interest with redox reagent (e.g., manganese or copper salts as oxidation catalysts) (see column 7, lines 21-22), and a mild detergent as is described by the reference incorporated, i.e., EP 43322 (see column 4, lines 46-52) which teaches that the mild detergent is non-ionic detergent, e.g., Tween (see page 5, line 45 of EP 433225) (*note that Tween that is a polyoxyethylene derivative*); and (**b**) incubating the above refolding reaction in order to refold the peptide that is recombinantly produced (see column 7, line10-17 and lines 30-36). Thus, the Builder et al. teaching anticipates claims 1, 3-4 and 8 of the current application.

Builder et al. teach that the peptide concentration for the refolding reaction is about 0.1 to 15 mg/ml; considering that the relaxin molecular weight is approximately 8,000; then, 15 mg/ml would give rise to 1.87 mM concentration of relaxin peptide. In addition, Builder et al. teach that the redox reagent, i.e., manganese or copper salts is about 15 μM. The above Builder et al teaching as to the method of refolding is thus applicable to claims 13, 15-16 and 18 of the current application.

As for redox reagent, Builder et al. teach that the alternative redox being used in the refolding reaction is 2-mercaptoethanol or cysteine (see column 18, lines 6-12), as applied to claims 7 and 20 of the current application.

Builder et al. teach that the refolding is typically carried out at about 0 –45 °C (see column 22, lines 54-55), as applied to the application claims 10 and 22.

Also, Builder et al. teach that the refolding reaction is carried out at pH 7-12 ("Summary of Invention" at column 6), as applied to claims 11 and 23 of the current application.

Further, Builder et al. teach that the said refolding reaction employs a cosolvent, i.e., polar aprotic solvent (see column 6, line 57), e.g., isopropanol, in an amount of 5- 40% (v/v) (see column 6, line 57), as applied to claims 2, 6, 14 and 18 of the current application.

The claims 1-11, 25 and 27-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Kljavin I. J. et al. (US Pat. No. 6331523).

Kljavin et al. teach a method of refolding a peptide (FGF5) containing disulfide from an aggregated (insoluble) form (see column 16) comprising (**a**) the peptide being subject to the refolding condition comprising (i) a mild detergent which is non-ionic detergent, e.g., Tween-80 (a polyoxylethylene derivative) or dodecyl-β-maltoside (see column 17, lines 57-62), and (ii) a sulfhydryl/disulfide redox reagent, e.g., oxidized (GSSH) and reduced (GSH) glutathione (see column 18), and (**b**) incubating said peptide with the refolding reagents comprising the components of (i) and (ii) in order for refolding said peptide. The Kljavin et al. teaching anticipates claims 1, 3-5 and 7-9 of the current application. Note that the Kljavin's patent is an anticipatory art over the instant claims *because* claim 1 sets forth peptide which comprises 5 –55 amino acids; such the claim language is open-ended and renders the claims so broad that it encompasses a heterologous portion(s) in addition to the peptide fragment of 5 to 55 amino

acids, and *because* the Kljavin's peptide is sulfhydryl/disulfide-rich segments (see page 18, lines 33-42).

Kljavin et al. teach that the said method further comprises biosynthesizing the peptide (in *E.coli*) and isolating the biosynthesized peptide *via* separating the peptide that exists in an *refractile body* using centrifugation (see column 16, lines 40-67), and, following the refolding reaction, the refolded peptide is purified by chromatography (see column 18, lines 24-32). The above Kljavin's teaching meets the limitation set forth in claim 25. Thus, the application claims 25, 27, 29-31 and 33-35 are also anticipated by the above-stated Kljavin' teachings.

Also, Kljavin et al. teach that cosolvent, e.g., ethanol, is used for the above refolding process (see column 18, lines 17-18), as applied to claims 2, 6, 28 and 32 of the current application.

Further, Kljavin et al. teach pH and temperature condition for the refolding, i.e., pH 8 and 4 °C (see column 17, lines 23-30), as applied to claims 10, 11, 36 and 37 of the current application.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this

application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

S.W.L

Samuel Wei Liu, Ph.D.

February 17, 2004

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER